

# MELODETTA 24 FE- norethindrone acetate and ethinyl estradiol and ferrous fumarate

## Amneal Pharmaceuticals NY LLC

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### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MELODETTA 24 FE safely and effectively. See full prescribing information for MELODETTA 24 FE.

**MELODETTA™ 24 FE (norethindrone acetate and ethinyl estradiol tablets and ferrous fumarate tablets), for oral use**

**Initial U.S. Approval: 1968**

#### **WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS**

*See full prescribing information for complete boxed warning.*

- **Women over 35 years old who smoke should not use Melodetta 24 Fe (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use (4)**

#### ----- RECENT MAJOR CHANGES -----

Contraindications (4)

08/2017

Warnings (5.3)

08/2017

#### ----- INDICATIONS AND USAGE -----

- Melodetta™ 24 Fe is an estrogen/progestin COC indicated for use by women to prevent pregnancy (1)
- The efficacy in women with a body mass index of more than 35 kg/m<sup>2</sup> has not been evaluated (1, 8.8)

#### ----- DOSAGE AND ADMINISTRATION -----

- One tablet daily chewed and swallowed or swallowed whole taken at the same time of day. Follow with 8 ounces of water (2.1)
- Take one tablet by mouth at the same time every day for 28 days (2.1)
- Take tablets in the order directed on the blister pack (2.1)
- Tablets may be administered without regard to meals (12.3)

#### ----- DOSAGE FORMS AND STRENGTHS -----

Melodetta 24 Fe consists of 28 tablets in the following order (3):

- 24 white chewable tablets (active), each containing 1 mg norethindrone acetate and 20 mcg ethinyl estradiol
- 4 brown tablets (non-hormonal placebo), each containing 75 mg ferrous fumarate, which do not serve any therapeutic purpose

#### ----- CONTRAINDICATIONS -----

- A high risk of arterial or venous thrombotic diseases (4)
- Breast cancer or other estrogen-or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

#### ----- WARNINGS AND PRECAUTIONS -----

- Vascular risks: Stop Melodetta 24 Fe if a thrombotic event occurs. Stop at least 4 weeks before through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding (5.1)
- Liver disease: Discontinue if jaundice occurs (5.2)
- High blood pressure: Do not prescribe for women with uncontrolled hypertension or hypertension with vascular disease (5.3)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Melodetta 24 Fe. Consider an alternative contraceptive method for women with uncontrolled dyslipidemia (5.5)
- Headache: Evaluate significant change in headaches and discontinue if indicated (5.6)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea (5.7)

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#### **ADVERSE REACTIONS**

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- The most common adverse reactions in clinical trials (greater than or equal to 2%) were: headache, vaginal candidiasis, nausea, menstrual cramps, breast tenderness, bacterial vaginitis, abnormal cervical smear, acne, mood swings, and weight gain. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

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#### **DRUG INTERACTIONS**

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- Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up method or alternative method of contraception when enzyme inducers are used with COCs (7.1)

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#### **USE IN SPECIFIC POPULATIONS**

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- Nursing mothers: Not recommended; can decrease milk production (8.3)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 12/2020**

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## **FULL PRESCRIBING INFORMATION**

### **WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS**

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke [see *Contraindications (4)*].

## **1 INDICATIONS AND USAGE**

Melodetta™ 24 Fe is indicated for use by females of reproductive age to prevent pregnancy [see *Clinical Studies (14)*].

The efficacy of Melodetta 24 Fe in women with a body mass index (BMI) of more than 35 kg/m<sup>2</sup> has not been evaluated.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 How to Take Melodetta 24 Fe**

To achieve maximum contraceptive effectiveness, Melodetta 24 Fe must be taken exactly as directed. Instruct patients to take one tablet by mouth at the same time every day. The tablet may be chewed and swallowed or swallowed whole. The patient should drink a full glass (8 ounces) of water immediately after the white tablets are chewed or swallowed whole. Tablets must be taken in the order directed on the blister pack. Tablets should not be skipped or taken at intervals exceeding 24 hours. For patient

instructions for missed tablets, *[see FDA-approved patient labeling]*. Melodetta 24 Fe may be administered without regard to meals *[see Clinical Pharmacology (12.3)]*.

## **2.2 How to Start Melodetta 24 Fe**

Instruct the patient to begin taking Melodetta 24 Fe either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

### *Day 1 Start*

During the first cycle of Melodetta 24 Fe use, instruct the patient to take one white Melodetta 24 Fe tablet daily, beginning on Day one (1) of her menstrual cycle (the first day of menstruation is Day one). She should take one white Melodetta 24 Fe tablet daily for 24 consecutive days, followed by one brown ferrous fumarate tablet daily on days 25 through 28. Melodetta 24 Fe should be taken in the order directed on the package at the same time each day. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days if she starts taking Melodetta 24 Fe on a day other than the first day of her menstrual cycle. The possibility of ovulation and conception prior to initiation of medication should be considered.

### *Sunday Start*

During the first cycle of Melodetta 24 Fe use, instruct the patient to take one white Melodetta 24 Fe tablet daily, beginning on the first Sunday after the onset of her menstrual period. She should take one white Melodetta 24 Fe tablet daily for 24 consecutive days, followed by one brown ferrous fumarate tablet daily on days 25 through 28. Melodetta 24 Fe should be taken in the order directed on the package at the same time each day. Melodetta 24 Fe should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of Melodetta 24 Fe on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her white Melodetta 24 Fe tablets on the next day after ingestion of the last brown tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of Melodetta 24 Fe is started later than the day following administration of the last brown ferrous fumarate tablet, the patient should use another method of contraception until she has taken a white Melodetta 24 Fe tablet daily for 7 consecutive days.

For postpartum women who do not breastfeed or after a second trimester abortion, start Melodetta 24 Fe no earlier than 4 weeks postpartum due to the increased risk of thromboembolism. If the patient starts on Melodetta 24 Fe postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken Melodetta 24 Fe for 7 consecutive days.

Melodetta 24 Fe may be initiated immediately after a first-trimester abortion or miscarriage; if the patient starts Melodetta 24 Fe immediately, additional contraceptive measures are not needed.

## **2.3 Switching from another Hormonal Method of Contraception**

If the patient is switching from a combination hormonal method such as:

- Another pill
- Vaginal ring
- Patch
- Instruct her to take the first white Melodetta 24 Fe tablet on the day she would have taken her next COC pill. She should not continue taking the tablets from her previous birth control pack, and should not skip any days between packs. If she does not have a withdrawal bleed, rule out pregnancy before starting Melodetta 24 Fe.

- If she previously used a vaginal ring or transdermal patch, she should start using Melodetta 24 Fe on the day she would have resumed the previous product.

If the patient is switching from a progestin-only method such as a:

- Progestin-only pill
  - Implant
  - Intrauterine system
  - Injection
- She may switch any day from a progestin-only pill; instruct her to take the first white Melodetta 24 Fe tablet on the day she would have taken her next progestin-only pill. She should use a non-hormonal method of contraception for 7 consecutive days.
  - If switching from an implant or injection, start the first white Melodetta 24 Fe tablet on the day her next injection would have been due or on the day of removal of her implant.
  - If switching from an IUD, depending on the timing of removal, back-up contraception may be needed.

## 2.4 Advice in Case of Gastrointestinal Disturbances

If the patient vomits or has diarrhea (within 3 to 4 hours after she takes a white Melodetta 24 Fe tablet), she should follow the instructions in the “*What to Do if You Miss Tablets*” section [see FDA-approved patient labeling].

## 3 DOSAGE FORMS AND STRENGTHS

Melodetta 24 Fe is available in blister packs.

Each blister pack contains 28 tablets in the following order:

- 24 white, round, (active) chewable tablets debossed with “AN” on one side and “30” on the other side, and each containing 1 mg norethindrone acetate, USP and 20 mcg ethinyl estradiol, USP.
- 4 brown, round (non-hormonal placebo) tablets debossed with “AN” on one side and “364” on the other side, and each containing 75 mg ferrous fumarate. The ferrous fumarate tablets do not serve any therapeutic purpose.

## 4 CONTRAINDICATIONS

Do not prescribe Melodetta 24 Fe to women who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
- Smoke, if over age 35 [see Boxed Warning and Warnings and Precautions (5.1)]
- Have deep vein thrombosis or pulmonary embolism, now or in the past [see Warnings and Precautions (5.1)]
- Have cerebrovascular disease [see Warnings and Precautions (5.1)]
- Have coronary artery disease [see Warnings and Precautions (5.1)]
- Have thrombotic valvular or thrombotic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see Warnings and Precautions (5.1)]
- Have inherited or acquired hypercoagulopathies [see Warnings and Precautions (5.1)]
- Have uncontrolled hypertension [see Warnings and Precautions (5.3)]
- Have diabetes mellitus with vascular disease [see Warnings and Precautions (5.5)]
- Have headaches with focal neurological symptoms or have migraine headaches with aura
- All women over age 35 with migraine headache [see Warnings and Precautions (5.6)]

- Liver tumors, benign or malignant, or liver disease [*see Warnings and Precautions (5.2)*]
- Undiagnosed abnormal uterine bleeding [*see Warnings and Precautions (5.7)*]
- Pregnancy, because there is no reason to use COCs during pregnancy [*see Warnings and Precautions (5.8)* and *Use in Specific Populations (8.1)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [*see Warnings and Precautions (5.10)*]
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations [*see Warnings and Precautions (5.3)*]

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Melodetta 24 Fe if an arterial or deep venous thrombotic event (VTE) occurs. Stop Melodetta 24 Fe if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

If feasible, stop Melodetta 24 Fe at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE.

Start Melodetta 24 Fe no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 per 10,000 woman-years. The risk of VTE is highest during the first year of use of a COC. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

Use of COCs also increases the risk of arterial thrombosis such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest in older (greater than 35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with underlying risk factors.

Use COCs with caution in women with cardiovascular disease risk factors.

### 5.2 Liver Disease

#### Impaired Liver Function

Do not use Melodetta 24 Fe in women with acute viral hepatitis or severe (decompensated) cirrhosis of the liver [*see Contraindications (4)*]. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue Melodetta 24 Fe if jaundice develops.

#### Liver Tumors

Melodetta 24 Fe is contraindicated in women with benign and malignant liver tumors [*see Contraindications (4)*]. Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases per 100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (greater than 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

### 5.3 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as COCs. Discontinue Melodetta 24 Fe prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir [see *Contraindications (4)*]. Melodetta 24 Fe can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

## **5.4 High Blood Pressure**

Melodetta 24 Fe is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease [see *Contraindications (4)*]. For women with well-controlled hypertension, monitor blood pressure and stop Melodetta 24 Fe if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

## **5.5 Gallbladder Disease**

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs may also worsen existing gallbladder disease.

A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC-related cholestasis.

## **5.6 Carbohydrate and Lipid Metabolic Effects**

Carefully monitor prediabetic and diabetic women who are taking Melodetta 24 Fe. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemias. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

## **5.7 Headache**

If a woman taking Melodetta 24 Fe develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Melodetta 24 Fe if indicated.

Consider discontinuation of Melodetta 24 Fe in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) [see *Contraindications (4)*].

## **5.8 Bleeding Irregularities and Amenorrhea**

### *Unscheduled Bleeding and Spotting*

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Based on patient diaries from a clinical trial evaluating the safety and efficacy of a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets, 24% to 35% of women experienced unscheduled bleeding per cycle. A total of 10 subjects out of 743 (1.3%) discontinued due to bleeding or spotting.

### *Amenorrhea and Oligomenorrhea*

Women who are not pregnant and use Melodetta 24 Fe may experience amenorrhea. In the clinical trial with a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets and ferrous fumarate tablets, 22% to 36% of the women using norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets and ferrous fumarate tablets experienced amenorrhea in at least one of 6 cycles of use. Some women may experience post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

### **5.9 COC Use before or during Early Pregnancy**

Extensive epidemiologic studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue Melodetta 24 Fe if pregnancy is confirmed.

Administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy [*see Use in Specific Populations (8.1)*].

### **5.10 Depression**

Carefully observe women with a history of depression and discontinue Melodetta 24 Fe if depression recurs to a serious degree.

### **5.11 Carcinoma of the Breasts and Cervix**

Melodetta 24 Fe is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally-sensitive [*see Contraindications (4)*].

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

### **5.12 Effect on Binding Globulins**

The estrogen component of COCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormones or cortisol therapy may need to be increased.

### **5.13 Monitoring**

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

### **5.14 Hereditary Angioedema**

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

### **5.15 Chloasma**



Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking Melodetta 24 Fe.

## 6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events [*see Warnings and Precautions (5.1)*]
- Liver disease [*see Warnings and Precautions (5.2)*]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

### 6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data presented in Section 6.1 are from a clinical trial conducted with a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets. Melodetta 24 Fe is bioequivalent to these norethindrone acetate/ethinyl estradiol tablets.

Common Adverse Reactions (Greater Than or Equal to 2% of all Treated Subjects): The most common adverse reactions reported by at least 2% of the 743 women using norethindrone acetate/ethinyl estradiol tablets were the following, in order of decreasing incidence: headache (6.3%), vaginal candidiasis (6.1%), nausea (4.6%), menstrual cramps (4.4%), breast tenderness (3.4%), bacterial vaginitis (3.1%), abnormal cervical smear (3.1%), acne (2.7%), mood swings (2.2%), and weight gain (2%).

Adverse Reactions Leading to Study Discontinuation: Among the 743 women using norethindrone acetate/ethinyl estradiol tablets, 46 women (6.2%) withdrew because of an adverse event. Adverse events occurring in 3 or more subjects leading to discontinuation of treatment were, in decreasing order: abnormal or irregular bleeding (1.3%), nausea (0.8%), menstrual cramps (0.5%), and increased blood pressure (0.4%).

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

Adverse reactions are grouped into System Organ Classes.

Vascular disorders: thrombosis/embolism (coronary artery, pulmonary, cerebral, deep vein).

Hepatobiliary disorders: cholelithiasis, cholecystitis, hepatic adenoma, hemangioma of liver.

Immune system disorders: hypersensitivity reaction.

Skin and subcutaneous disorders: alopecia, rash (generalized and allergic), pruritus, skin discoloration.

GI disorders: nausea, vomiting, abdominal pain.

Musculoskeletal and connective tissue disorders: myalgia.

Eye disorders: blurred vision, visual impairment, corneal thinning, change in corneal curvature (steepening).

Infections and infestations: fungal infection, vaginal infection.

Investigations: change in weight or appetite (increase or decrease), fatigue, malaise, peripheral edema, blood pressure increased.

Nervous system disorders: headache, dizziness, migraine, loss of consciousness.

Psychiatric disorders: mood swings, depression, insomnia, anxiety, suicidal ideation, panic attack, changes in libido.

Renal and urinary disorders: cystitis-like syndrome.

Reproductive system and breast disorders: breast changes (tenderness, pain, enlargement, and secretion), premenstrual syndrome, dysmenorrhea.

Cardiovascular: chest pain, palpitations, tachycardia, myocardial infarction.

## 7 DRUG INTERACTIONS

Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

No drug-drug interaction studies were conducted with Melodetta 24 Fe.

### 7.1 Effects of Other Drugs on Combined Oral Contraceptives

**Substances diminishing the efficacy of COCs:** Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

**Substances increasing the plasma concentrations of COCs:** Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone concentrations.

**Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:** Significant changes (increase or decrease) in the plasma concentrations of the estrogen and progestin have been noted in some cases of co-administration of HIV/HCV protease inhibitors or of non-nucleoside reverse transcriptase inhibitors.

**Antibiotics:** There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

### 7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing ethinyl estradiol may inhibit the metabolism of other compounds. COCs have been

shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

### **7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation**

Do not co-administer Melodetta 24 Fe with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations [*see Warnings and Precautions (5.3)*].

### **7.4 Interference with Laboratory Tests**

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

### **8.3 Nursing Mothers**

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

### **8.4 Pediatric Use**

Safety and efficacy of Melodetta 24 Fe have been established in women of reproductive age. Efficacy is expected to be the same in postpubertal adolescents under the age of 18 years as for users 18 years and older. Use of this product before menarche is not indicated.

### **8.5 Geriatric Use**

Melodetta 24 Fe has not been studied in postmenopausal women and is not indicated in this population.

### **8.6 Renal Impairment**

The pharmacokinetics of Melodetta 24 Fe has not been studied in subjects with renal impairment.

### **8.7 Hepatic Impairment**

The pharmacokinetics of Melodetta 24 Fe has not been studied in subjects with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded [*see Contraindications (4)* and *Warnings and Precautions (5.2)*].

## 8.8 Body Mass Index

The safety and efficacy of Melodetta 24 Fe in women with a body mass index (BMI) greater than 35 kg/m<sup>2</sup> has not been evaluated [see *Clinical Studies (14)*].

## 10 OVERDOSAGE

There have been no reports of serious ill effects from overdose of oral contraceptives, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

## 11 DESCRIPTION

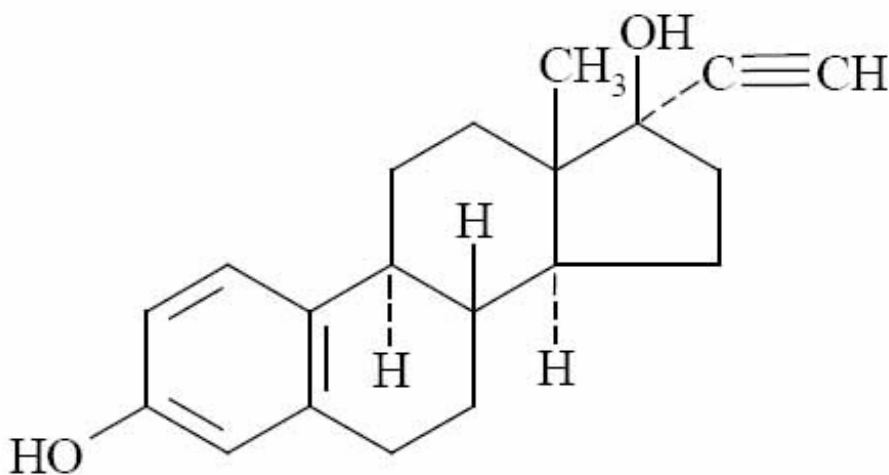
Melodetta™ 24 Fe provides an oral contraceptive regimen consisting of 24 white active chewable tablets that contain the active ingredients, followed by 4 brown non-hormonal placebo tablets as specified below:

- 24 white, round tablets each containing 1 mg norethindrone acetate, USP and 20 mcg ethinyl estradiol, USP.
- 4 brown, round tablets each containing 75 mg ferrous fumarate.

Each white active chewable tablet also contains the following inactive ingredients: acacia, confectioner's sugar, lactose monohydrate, magnesium stearate, microcrystalline cellulose and talc.

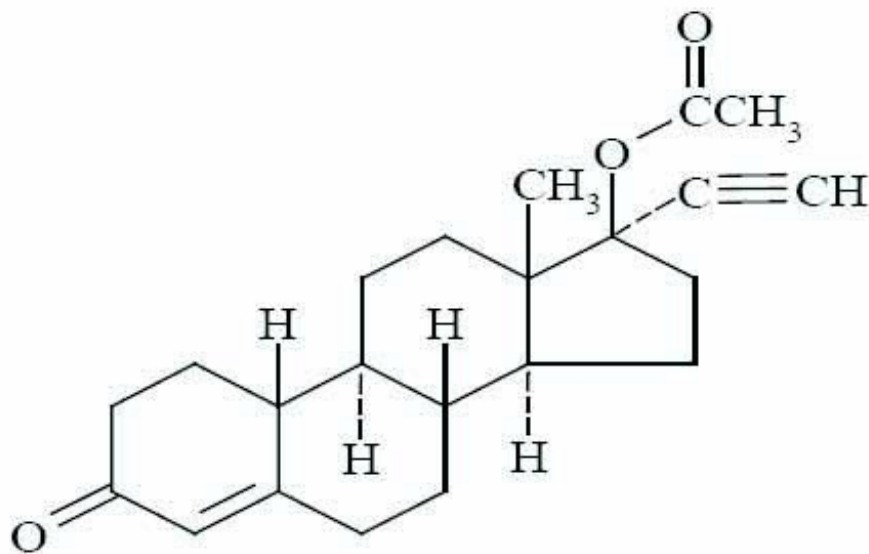
Each brown placebo tablet contains ferrous fumarate, croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, povidone, spearmint flavor and sucralose. The ferrous fumarate tablets do not serve any therapeutic purpose.

The empirical formula of ethinyl estradiol, USP is C<sub>20</sub>H<sub>24</sub>O<sub>2</sub> and the structural formula is:



The chemical name of ethinyl estradiol, USP is [19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 $\alpha$ )-]. The molecular weight of ethinyl estradiol, USP is 296.40.

The empirical formula of norethindrone acetate, USP is C<sub>22</sub>H<sub>28</sub>O<sub>3</sub> and the structural formula is:



The chemical name of norethindrone acetate, USP is [19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17 $\alpha$ )-]. The molecular weight of norethindrone acetate, USP is 340.46.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

### 12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Melodetta 24 Fe.

### 12.3 Pharmacokinetics

#### *Absorption*

In a single-dose, two-way, crossover clinical study conducted in 35 healthy, non-smoking premenopausal women under fasting condition, Melodetta 24 Fe tablet chewed and swallowed was bioequivalent to norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablet (24-day regimen tablets) swallowed whole based on the exposure (AUC) and peak concentration ( $C_{\max}$ ) of norethindrone and ethinyl estradiol.

Norethindrone acetate appears to be completely and rapidly deacetylated to norethindrone after oral administration, because the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate and ethinyl estradiol are absorbed from Melodetta 24 Fe tablets (chewed and swallowed), with maximum plasma concentrations of norethindrone and ethinyl estradiol occurring at 1 hr (range: 0.7 to 2.5 hrs) and 1.3 hr (range: 1 to 2.5 hrs) post-dose, respectively. Both are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for norethindrone and 43% for ethinyl estradiol.

The plasma norethindrone and ethinyl estradiol pharmacokinetics following single-dose administrations of Melodetta 24 Fe tablets (chewed and swallowed) in 35 healthy female subjects are provided in Figures 1 and 2, and Table 1.

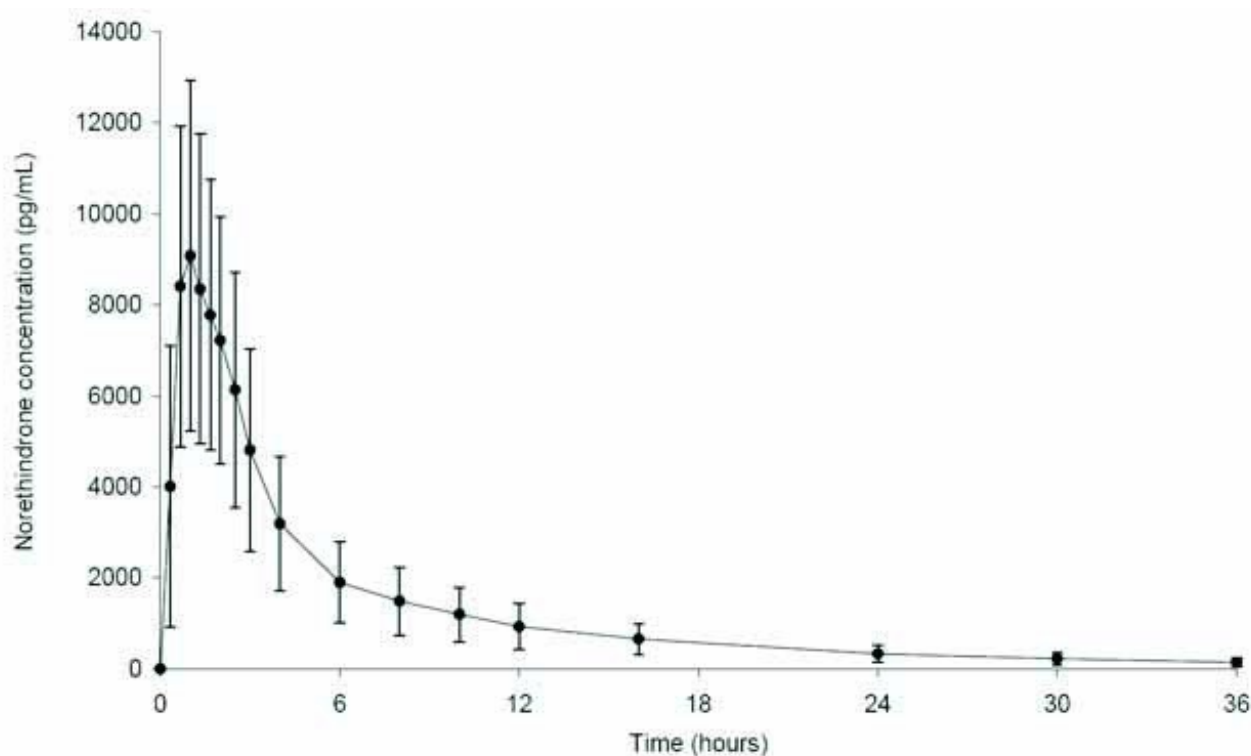
Following multiple-dose administration of norethindrone acetate/ethinyl estradiol tablets (swallowed whole) in 17 healthy female subjects, mean maximum concentrations of norethindrone and ethinyl estradiol were increased by 95% and 27%, respectively, as compared to single-dose administration.

Mean norethindrone and ethinyl estradiol exposures (AUC values) were increased by 164% and 51% respectively, as compared to single-dose administration of norethindrone acetate/ethinyl estradiol tablets.

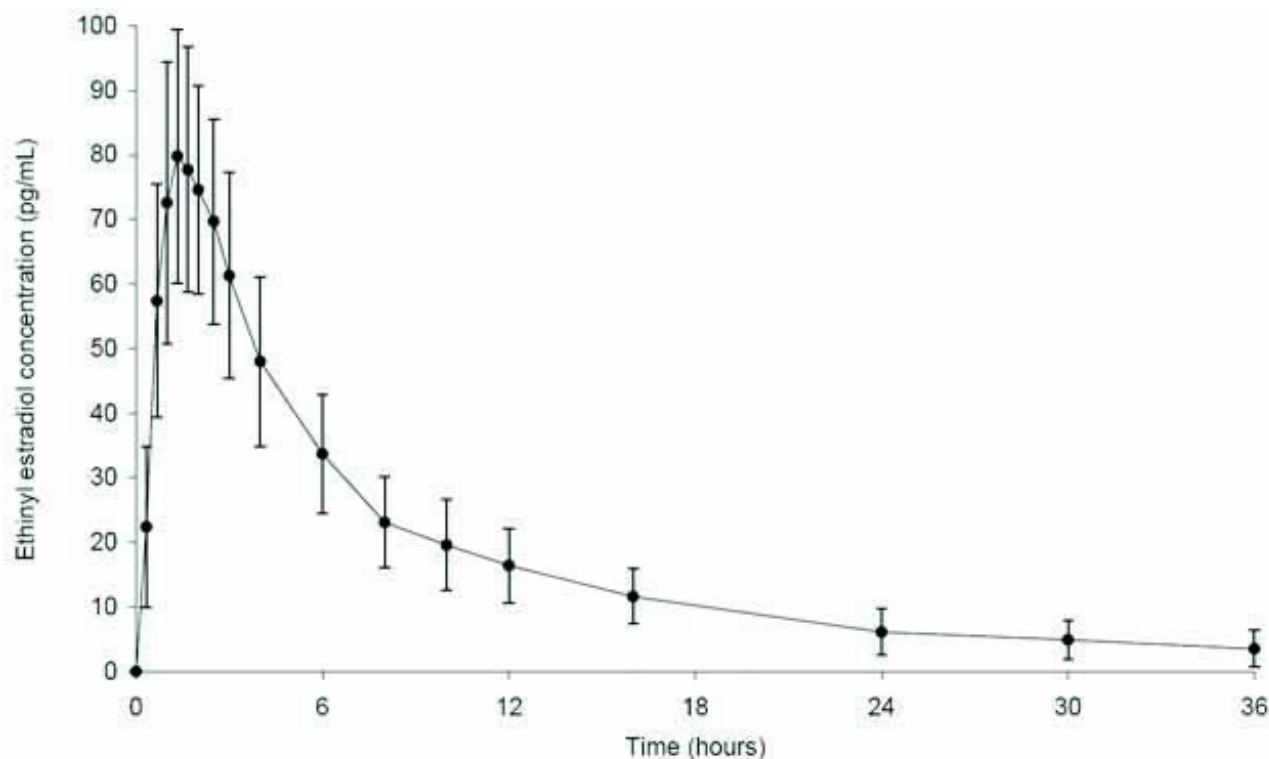
Steady-state with respect to norethindrone was reached by Day 17 and steady-state with respect to ethinyl estradiol was reached by Day 13.

Mean SHBG concentrations were increased by 150% from baseline (57.5 nmol/L) to 144 nmol/L at steady-state.

**Figure 1. Mean ( $\pm$  Standard Deviation) Plasma Norethindrone Concentration-Time Profile Following Single-Dose Oral Administration of Melodetta 24 Fe Tablets (chewed and swallowed) to Healthy Female Volunteers under Fasting Conditions (n = 35)**



**Figure 2. Mean ( $\pm$  Standard Deviation) Plasma Ethinyl Estradiol Concentration-Time Profile Following Single-Dose Oral Administration of Melodetta 24 Fe Tablets(chewed and swallowed) to Healthy Female Volunteers under Fasting Conditions (n = 35)**



**Table 1. Summary of Norethindrone (NE) and Ethinyl Estradiol (EE) Pharmacokinetics Following Single-Dose Oral Administration of Melodetta 24 Fe Tablets (chewed and swallowed) to Healthy Female Volunteers Under Fasting Conditions (n = 35)**

Analyte	Arithmetic Mean <sup>a</sup> (% CV) by Pharmacokinetic Parameter				
	C <sub>max</sub> (pg/mL)	t <sub>max</sub> (hr)	AUC <sub>(0-tldc)</sub> (pg/mL•h)	AUC <sub>(0-inf)</sub> (pg/mL•h)	t <sub>1/2</sub> (hr)
NE	10200 (36)	1.03 (0.67 to 2.50)	48620 (40)	49250 (40)	8.58
EE	84.7 (24)	1.33 (1 to 2.50)	677.5 (33)	741.6 (33)	9.68

C<sub>max</sub> = Maximum plasma concentration

t<sub>max</sub> = Time of C<sub>max</sub>

AUC<sub>(0-tldc)</sub> = Area under plasma concentration versus time curve from 0 to tldc, the time of last determinable concentration

AUC<sub>(0-inf)</sub> = Area under the plasma concentration versus time curve from time 0 to infinity

t<sub>1/2</sub> = Terminal phase half-life

% CV = Coefficient of Variation (%)

<sup>a</sup> The harmonic mean (0.693/mean terminal phase rate constant) is reported for t<sub>1/2</sub>, and the median (range) is reported for t<sub>max</sub>

#### *Food Effect*

Melodetta 24 Fe tablets may be administered without regard to meals.

A single-dose administration of norethindrone acetate/ethinyl estradiol tablets with food decreased the maximum concentration of norethindrone by 51% and increased the extent of absorption by 15% and decreased the maximum concentration of ethinyl estradiol by 51% but not the extent of absorption.

#### *Distribution*

Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (greater than 95%); norethindrone binds to both albumin and SHBG, whereas ethinyl estradiol binds only to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis.

#### *Metabolism*

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.

Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation.

#### *Excretion*

Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites. Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg). Steady-state elimination half-lives of norethindrone and ethinyl estradiol following administration of norethindrone acetate/ethinyl estradiol tablets are approximately 8 hours and 14 hours, respectively.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

*[See Warnings and Precautions (5.2, 5.11) and Use in Specific Populations (8.1).]*

## **14 CLINICAL STUDIES**

The data presented in Section 14 are from a clinical trial conducted with a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets. Melodetta 24 Fe is bioequivalent to these norethindrone acetate/ethinyl estradiol tablets.

In a clinical study, 743 women 18 to 45 years of age were studied to assess the efficacy of norethindrone acetate/ethinyl estradiol tablets, for up to six 28-day cycles providing a total of 3,823 treatment-cycles of exposure. The racial demographic of all enrolled women was: 70% Caucasian, 16% African-American, 10% Hispanic, 2% Asian and 2% Other. Women with body mass index (BMI) greater than 35 kg/m<sup>2</sup> were excluded from the study. The weight range for those women treated was 90 to 260 pounds, with a mean weight of 147 pounds. Among the women in the study, about 40% had not used hormonal contraception immediately prior to enrolling in this study.

A total of 583 women completed 6 cycles of treatment. There were a total of 5 on-treatment pregnancies in 3,565 treatment cycles during which no backup contraception was used. The Pearl Index for norethindrone acetate and ethinyl estradiol tablets was 1.82 (95% confidence interval 0.59 to 4.25).

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### **16.1 How Supplied**



Melodetta™ 24 Fe (norethindrone acetate and ethinyl estradiol tablets, 1 mg/20 mcg and ferrous fumarate tablets, 75 mg) are available in blister cards (dispensers) containing 28 tablets (NDC 69238-1031-6):

Cartons of 3 blister cards (dispensers)                      NDC 69238-1031-7

Each blister card contains 28 tablets in the following order:

- 24 white to off-white, round, uncoated, unscored, flat-faced beveled edge (active) tablets debossed with “AN” on one side and “30” on the other side, and each containing 1 mg norethindrone acetate, USP and 20 mcg ethinyl estradiol, USP.
- 4 brown, round, uncoated, unscored, flat-faced, beveled edge (non-hormonal placebo) tablets debossed with “AN” on one side and “364” on the other side, and each containing 75 mg ferrous fumarate. The ferrous fumarate tablets do not serve any therapeutic purpose.

## 16.2 Storage Conditions

Store at 20° to 25° C (68° to 77° F); excursions permitted between 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature].

Keep this drug and all drugs out of the reach of children.

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Counsel patients on the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from COC use, and women who are over 35 years old and smoke should not use COCs.
- Melodetta 24 Fe does not protect against HIV infection (AIDS) and other sexually transmitted infections.
- The Warnings and Precautions associated with COCs.
- Melodetta 24 Fe is not to be used during pregnancy; if pregnancy occurs during use of Melodetta 24 Fe, instruct the patient to stop further intake.
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event tablets are missed. See “*What to Do if You Miss Tablets*” section in *FDA-approved patient labeling*.
- Use a back-up or alternative method of contraception when enzyme inducers are used with Melodetta 24 Fe.
- COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Women who start COCs postpartum, and who have not yet had a period, should use an additional method of contraception until they have taken a white tablet for 7 consecutive days.
- Amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.

Distributed by:

**Amneal Pharmaceuticals LLC**

Bridgewater, NJ 08807

Rev. 09-2017-05

## FDA-Approved Patient Labeling

**Guide for Using Melodetta™ 24 Fe (meh loe deh' tah)**

**(norethindrone acetate and ethinyl estradiol tablets and ferrous fumarate tablets)**

**WARNING  
TO WOMEN  
WHO  
SMOKE**  
**Do not use  
Melodetta 24  
Fe if you  
smoke  
cigarettes and  
are over 35  
years old.**  
**Smoking  
increases your  
risk of serious  
cardiovascular  
side effects  
(heart and  
blood vessel  
problems)  
from birth  
control pills,  
including  
death from  
heart attack,  
blood clots or  
stroke. This  
risk increases  
with age and  
the number of  
cigarettes you  
smoke.**

Birth control pills help to lower the chances of becoming pregnant when taken as directed. They do not protect against HIV infection (AIDS) and other sexually transmitted infections.

### **What is Melodetta 24 Fe?**

Melodetta 24 Fe is a birth control pill. It contains two female hormones, an estrogen called ethinyl estradiol, and a progestin called norethindrone acetate.

### **How well do Melodetta 24 Fe work?**

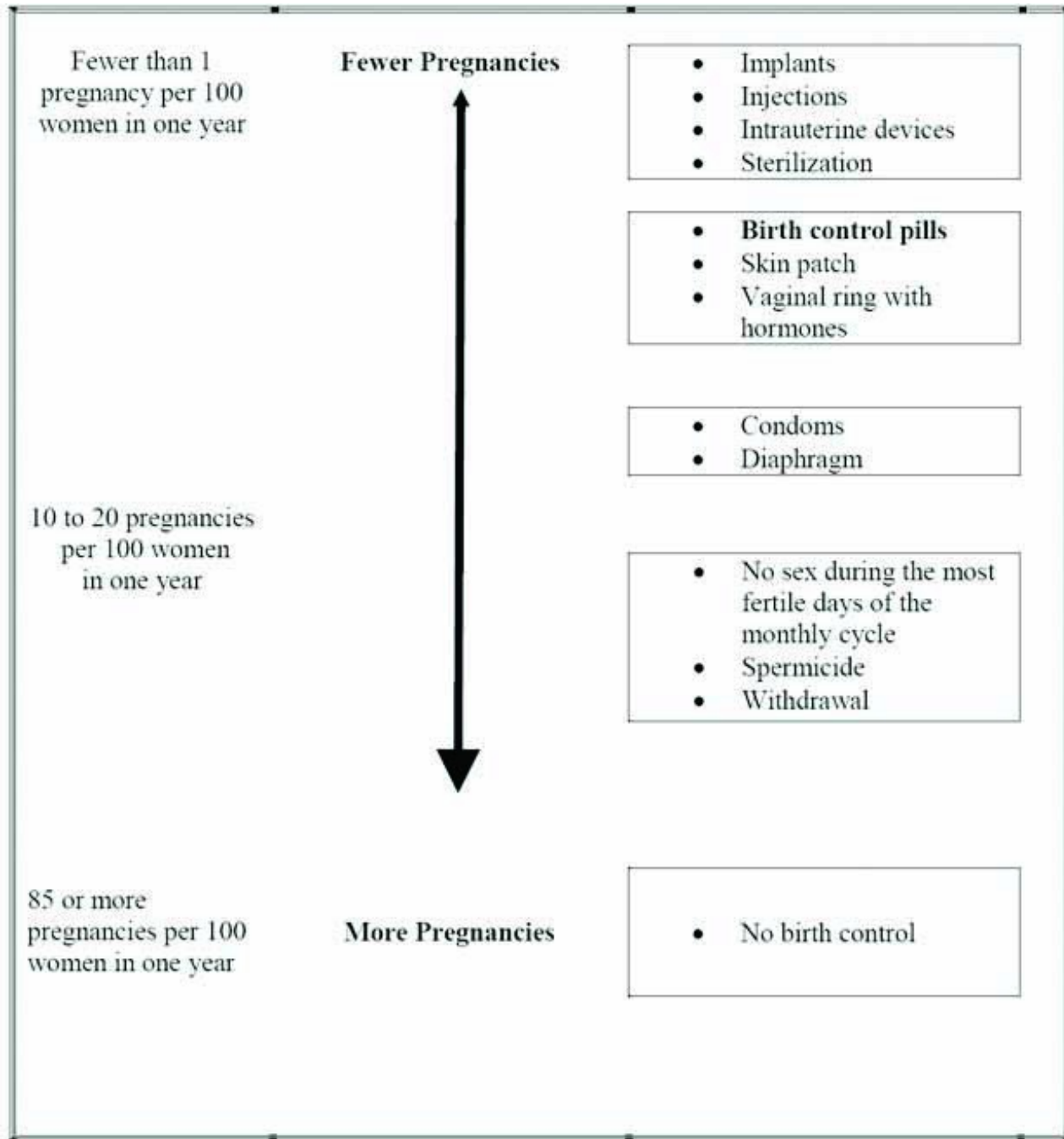
Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of one clinical study of a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets lasting six months, about 1 to 4 out of 100 women may get pregnant during the first year they use Melodetta 24 Fe.

Women with a BMI above 35 kg/m<sup>2</sup> were not studied in the clinical trial, so it is not known how well Melodetta 24 Fe protects against pregnancy in such women. If you are overweight, discuss with your healthcare provider whether Melodetta 24 Fe is the best choice for you.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart

shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



### How do I take Melodetta 24 Fe?

1. **Be sure to read these directions** before you start taking your tablets or anytime you are not sure what to do.
2. The tablets may be chewed and swallowed or swallowed whole. You should drink a full glass (8 ounces) of water immediately after chewing or swallowing.
3. The right way to take the tablet is to take one tablet every day at the same time in the order directed on the package. Melodetta 24 Fe can be taken without regard to meals.

If you miss tablets you could get pregnant. This includes starting the pack late. The more tablets you miss, the more likely you are to get pregnant. See "What to Do if You Miss Tablets" below.

4. Many women have spotting or light bleeding at unexpected times, or may feel sick to their stomach

during the first 1 to 3 packs of tablets.

If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the tablets. The problem will usually go away. If it does not go away, check with your healthcare provider.

5. Missing tablets can also cause spotting or light bleeding, even when you make up these missed tablets.

On the days you take two tablets, to make up for missed tablets, you could also feel a little sick to your stomach.

6. If you have vomiting (within 3 to 4 hours after you take your tablet), you should follow the instructions for "What to Do if You Miss Tablets". If you have diarrhea or if you take certain medicines, including some antibiotics and some herbal products such as St. John's Wort, your tablets may not work as well.

Use a back-up method (such as condoms and spermicides) until you check with your healthcare provider.

7. If you have trouble remembering to take Melodetta 24 Fe, talk to your healthcare provider about how to make tablet-taking easier or about using another method of birth control.
8. **If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.**

#### Before You Start Taking Your Melodetta 24 Fe Tablets

1. Decide What Time of Day You Want to Take Your Tablet. It is important to take Melodetta 24 Fe tablets in the order directed on the package at the same time every day. Melodetta 24 Fe can be taken without regard to meals.

2. Look at Your Tablet Pack – It has 28 Tablets

The Melodetta 24 Fe pack has 24 "active" white tablets (with hormones) to be taken for 24 days, followed by 4 "reminder" brown tablets (without hormones) to be taken for the next four days.

3. Also look for:

- a) Where on the pack to start taking tablets,
- b) In what order to take the tablets (follow the arrows shown in the picture above)
- c) The week numbers as shown in the picture above.

4. Be sure you have ready at all times

- a) another kind of birth control (such as a condoms and spermicide) to use as a back-up in case you miss tablets, and
- b) an extra, full tablet pack.

#### When to Start the First Pack of Tablets

You have a choice for which day to start taking your first pack of tablets. Decide with your healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

Day 1 Start:

- 1. Pick the day label strip that starts with the first day of your period (this is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins).
- 2. Place this day label strip on the tablet dispenser over the area that has the days of the week (starting with Sunday) printed on the plastic.
- 3. Take the first white tablet of the pack during the first 24 hours of your period.
- 4. You will not need to use a back-up method of birth control, since you are starting the tablet at the beginning of your period. However, if you start Melodetta 24 Fe later than the first day of your period, you should use another method of birth control (such as a condom and spermicide) as a back-

up method until you have taken 7 white tablets.

#### Sunday Start:

1. Take the first white tablet of the pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control (such as a condom and spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). This also applies if you start Melodetta 24 Fe after having been pregnant, and you have not had a period since your pregnancy.

#### When You Switch From a Different Birth Control Tablet or Capsule

When switching from another birth control pill, finish all the tablets or capsules, then Melodetta 24 Fe should be started on the same day that a new pack of the previous birth control tablet or capsule would have been started.

#### When You Switch From Another Type of Birth Control Method

When switching from a transdermal patch or vaginal ring, finish the 21 days of use, wait 7 days, then Melodetta 24 Fe should be started when the next application would have been due. When switching from an injection, Melodetta 24 Fe should be started when the next injection would have been due. When switching from an intrauterine device or an implant, Melodetta 24 Fe should be started on the day of removal.

#### What to Do During the Month

1. Take one tablet at the same time every day until the pack is empty.

Do not skip tablets even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).

2. Do not skip tablets even if you do not have sex very often.

When you finish a pack of tablets, start the next pack on the day after your last brown tablet. Do not wait any days between packs.

#### What to Do if You Miss Tablets

Melodetta 24 Fe may not be as effective if you miss any white tablets, especially if you miss the first few or the last few white tablets in a pack.

#### **If you miss 1 white tablet:**

1. Take the tablet as soon as you remember. Take the next tablet at your regular time. This means you may take two tablets in one day.
2. You do not need to use a back-up birth control method if you have sex.

#### **If you miss 2 white tablets in a row in week 1 OR week 2 of your pack:**

1. Take two tablets on the day you remember and two tablets the next day.
2. Then take one tablet a day until you finish the pack.
3. **You could become pregnant** if you have sex in the 7 days after you restart your tablets. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

#### **If you miss 2 white tablets in a row in week 3 or week 4 of your pack:**

1. **If you are a Day 1 Starter:**

Throw out the rest of the tablet pack and start a new pack that same day.

#### **If you are a Sunday Starter:**

Keep taking one tablet every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of tablets that same day.

2. **You could become pregnant** if you have sex in the 7 days after you restart your tablets. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.
3. You may not have your period this month but this is expected. **However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.**

**If you miss 3 or more white tablets in a row during any week:**

**1. If you are a Day 1 Starter:**

Throw out the rest of the tablet pack and start a new pack that same day.

**If you are a Sunday Starter:**

Keep taking 1 tablet every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of tablets that same day.

2. **You could become pregnant** if you have sex on the days when you missed tablets or during the first 7 days after you restart your tablets. You must use another birth control method (such as a condom and spermicide) as a back-up the next time you have sex and for the first 7 days after you restart your tablets.
3. You may not have your period this month but this is expected. **However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.**

**If you miss any of the 4 brown tablets in Week 4:**

1. Throw away the tablets you missed.
2. Keep taking one tablet each day until the pack is empty.
3. You do not need a back-up method.
4. Start the next pack of Melodetta 24 Fe as scheduled.

**Finally, if you are still not sure what to do about the tablets you have missed:**

1. Use a back-up method (such as a condom and spermicide) anytime you have sex.
2. Contact your healthcare provider and continue taking one active white tablet each day until otherwise directed.

**Who should not take Melodetta 24 Fe?**

Your healthcare provider will not give you Melodetta 24 Fe if you have:

- Ever had blood clots in your arms, legs (deep vein thrombosis), lungs (pulmonary embolism), or eyes (retinal thrombosis)
- Ever had a stroke
- Ever had a heart attack
- Certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- An inherited problem with your blood that makes it clot more than normal
- High blood pressure that medicine cannot control
- Diabetes with kidney, eye, nerve, or blood vessel damage
- Ever had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or have any migraine headache if you are over age 35.
- Ever had breast cancer or any cancer that is sensitive to female hormones
- Liver disease, including liver tumors
- Take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme “alanine aminotransferase” (ALT) in the blood

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are or suspect you are pregnant

- Have any unexplained bleeding from the vagina

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy, also called cholestasis of pregnancy.

Tell your healthcare provider if you have ever had any of the above conditions (your healthcare provider may recommend another method of birth control).

### **What else should I know about taking Melodetta 24 Fe?**

Birth control pills do **not** protect you against any sexually transmitted infection, including HIV, the virus that causes AIDS.

Do not skip any tablets, even if you do not have sex often.

**If you miss a period, you could be pregnant.** However, some women miss periods or have light periods on birth control pills, even when they are not pregnant. Contact your healthcare provider for advice if you:

- Think you are pregnant
- Miss one period and have not taken your birth control pills every day
- Miss two periods in a row

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects.

You should stop Melodetta 24 Fe at least four weeks before you have surgery and not restart it until at least two weeks after the surgery, due to an increased risk of blood clots.

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like Melodetta 24 Fe, may decrease the amount of milk you make. A small amount of the pill's hormones passes into breast milk.

Tell your healthcare provider about all medicines and herbal products that you take. Some medicines and herbal products may make birth control pills less effective, including:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

Use a back-up or alternative birth control method when you take medicines that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

If you have vomiting or diarrhea, your birth control pills may not work as well. Use another birth control method, like a condom and spermicide, until you check with your healthcare provider.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone.

If you are scheduled for any laboratory tests, tell your healthcare provider that you are taking birth control pills. Certain blood tests may be affected by birth control pills.

### **What are the most serious risks of taking Melodetta 24 Fe?**



Like pregnancy, birth control pills increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. This increased risk is highest when you first start taking birth control pills and when you restart the same or different birth control pills after not using them for a month or more.

It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke.

Some examples of serious blood clots are blood clots in the:

- Legs (deep vein thrombosis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

Women who take birth control pills may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

**Call your healthcare provider right away if you have:**

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain or pressure in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

**What are the common side effects of birth control pills?**

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat (cholesterol, triglyceride) levels in the blood
- Depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself
- Problems tolerating contact lenses
- Weight gain

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

### **Do birth control pills cause cancer?**

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

### **What should I know about my period when taking Melodetta 24 Fe?**

Irregular vaginal bleeding or spotting may occur while you are taking Melodetta 24 Fe. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your tablets on schedule. If the bleeding occurs in more than one cycle, is unusually heavy, or lasts for more than a few days, call your healthcare provider.

Some women may not have a menstrual period but this should not be cause for alarm as long as you have taken the tablets according to direction.

### **What if I miss my scheduled period when taking Melodetta 24 Fe?**

It is not uncommon to miss your period. However, if you go two or more months in a row without a period, or you miss your period after a month where you did not take all your tablets correctly, call your healthcare provider because you may be pregnant. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. Stop taking Melodetta 24 Fe if you are pregnant.

### **What if I want to become pregnant?**

You may stop taking the tablets whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the tablets.

### **General Advice about Melodetta 24 Fe**

Your healthcare provider prescribed Melodetta 24 Fe for you. Please do not share Melodetta 24 Fe with anyone else. Keep Melodetta 24 Fe out of the reach of children.

If you have concerns or questions, ask your healthcare provider. You may also ask your pharmacist for a more detailed label written for healthcare professionals.

For all medical inquiries contact Amneal Pharmaceuticals at 1-877-835-5472.

Distributed by:

**Amneal Pharmaceuticals LLC**

Bridgewater, NJ 08807

Rev. 08-2017-03

**PRINCIPAL DISPLAY PANEL**



1 Blister Pack Containing 28 Tablets

NDC 69238-1031-6



**Melodetta™ 24 Fe**  
(norethindrone acetate and  
ethinyl estradiol tablets  
and ferrous fumarate tablets\*)

**1 mg/20 mcg**

**Chewable**

*Melodetta™ 24 Fe, 1 mg/20 mcg  
provides 24 days of active therapy*

**This product (like all oral contraceptives) is intended  
to prevent pregnancy. It does not protect against  
HIV infection (AIDS) and other sexually transmitted  
diseases.**

**Not child resistant.**

**Rx only**

**This pouch contains one  
blister card of 28 tablets**



**LOT/EXP AREA**

Each white tablet contains norethindrone acetate, USP,  
1 mg; ethinyl estradiol, USP, 20 mcg; each brown tablet  
contains ferrous fumarate, 75 mg.  
**Usual Dosage:** One tablet daily. See Package  
Insert for Full Prescribing Information.

**This package is not child resistant.**


**Keep this and all drugs out of the reach of children.**

**Store** at 20° to 25°C (68° to 77°F); excursions permitted between  
15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].



Distributed by:  
**Amneal Pharmaceuticals LLC**  
Bridgewater, NJ 08807

Rev. 07-2017-01



N 3 69238 10316 8

START

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MON

TUE


WED


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FRI


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NDC 69238-1031-6




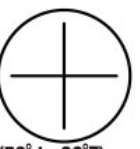




















Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F)






















[see USP Controlled Room Temperature].






















This package is not child resistant. Keep this and all drugs out of the reach of children. Rx Only


















Melodetta™ 24 Fe (norethindrone acetate and ethinyl estradiol tablets, 1 mg/20 mcg and ferrous fumarate tablets)



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This product (like all oral contraceptives)  
is intended to prevent pregnancy.  
It does not protect against HIV infection (AIDS)  
and other sexually transmitted infections.

MELODETTA 24 FE

norethindrone acetate and ethinyl estradiol and ferrous fumarate kit

Product Information

Product Type

HUMAN PRESCRIPTION DRUG

Item Code (Source)

NDC:69238-1031

Packaging

#

Item Code

Package Description

Marketing Start Date

Marketing End Date

1

NDC:69238-1031-7

3 in 1 CARTON

09/21/2017

1

NDC:69238-1031-6

1 in 1 BLISTER PACK; Type 0: Not a Combination Product

Quantity of Parts

Part #

Package Quantity

Total Product Quantity

Part 1

24

Part 2

4

Part 1 of 2

NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL

norethindrone acetate and ethinyl estradiol tablet, chewable

Product Information

Route of Administration

ORAL

Active Ingredient/Active Moiety

Ingredient Name

Basis of Strength

Strength

NORETHINDRONE ACETATE (UNII: 9S44LIC7OJ) (NORETHINDRONE - UNII:T18F433X4S)

NORETHINDRONE ACETATE

1 mg

ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)

ETHINYL ESTRADIOL

20 ug

Inactive Ingredients

Ingredient Name

Strength

ACACIA (UNII: 5C5403N26O)

SUGARCANE (UNII: 81H2R5AOH3)

LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)

MAGNESIUM STEARATE (UNII: 70097M6I30)

CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)

TALC (UNII: 7SEV7J4R1U)

Product Characteristics

<b>Color</b>	WHITE (white to off-white)	<b>Score</b>	no score
<b>Shape</b>	ROUND	<b>Size</b>	6 mm
<b>Flavor</b>		<b>Imprint Code</b>	AN;30
<b>Contains</b>			

## Marketing Information

<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
ANDA	ANDA207514	09/21/2017	

## Part 2 of 2

## INERT

inert tablet

## Product Information

<b>Route of Administration</b>	ORAL
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## Inactive Ingredients

<b>Ingredient Name</b>	<b>Strength</b>
FERROUS FUMARATE (UNII: R5L488RY0Q)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONE (UNII: FZ989GH94E)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	

## Product Characteristics

<b>Color</b>	BROWN	<b>Score</b>	no score
<b>Shape</b>	ROUND	<b>Size</b>	6 mm
<b>Flavor</b>	SPEARMINT	<b>Imprint Code</b>	AN;364
<b>Contains</b>			

## Marketing Information

<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
ANDA	ANDA207514	09/21/2017	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA207514	09/21/2017	

**Labeler** - Amneal Pharmaceuticals NY LLC (123797875)

**Establishment**

Name	Address	ID/FEI	Business Operations
Amneal Pharmaceuticals of New York, LLC		123797875	ANALYSIS(69238-1031) , LABEL(69238-1031) , MANUFACTURE(69238-1031) , PACK(69238-1031)

Revised: 12/2020

Amneal Pharmaceuticals NY LLC